REMARKS

Applicants have amended the first paragraph of the specification to indicate that the present application is a national stage filing of PCT/US2004/038670, filed November 18, 2004.

Applicants have canceled claims 11-20 and 33-36, without prejudice and amended claims 1, 2, 4, 6, 8, 10, 21, 22, 24-26, 28, and 30-32, without prejudice. Applicants reserve the right to pursue the deleted subject matter in one or more continuing applications.

The claim amendments have been made to clarify that which Applicants regard as the invention and correct editorial errors. Specifically, claims 1, 2, 4, 6, 8, 10, 21, 22, 24, 26, 28, and 30-32 have been amended to specify a concentration range for chlorobutanol. Support for these amendments can be found in the specification, for example, in paragraph [0025]. Claim 25 has been amended to replace "an" with "the" and to delete duplication of the word "is". Claim 30 has been amended to delete a duplication of a period at the end of the sentence.

No new matter has been added by these amendments.

After entry of the amendments, claims 1-10 and 21-32 will be pending.

Applicants respectfully request entry of the foregoing amendments and consideration of the following remarks.

Specification

The specification has been objected to because the Examiner alleges that the first paragraph must reference the PCT application from which the instant application entered national stage, i.e., indicate that the present application is a national stage filing of PCT/US2004/038670, filed November 18, 2004.

Without admitting to the propriety of the objection, Applicants have amended the first paragraph of the specification to indicate that the present application is a national stage filing of PCT/US2004/038670, filed November 18, 2004. However, Applicants respectfully submit that it is not necessary "to reference the international application number that was used to identify the application during international processing of the application by the international authorities prior to commencement of the national stage". See MPEP § 1893.03(c)III.

Accordingly, Applicants respectfully submit that objection has been obviated.

Claim Objections

Claims 30 and 34 were objected to because there are two periods at the end of each sentence.

Applicants have amended claim 30 to delete the second period and canceled claim 34.

Accordingly, Applicants respectfully submit that the objection has been obviated.

Claim Rejections – 35 USC § 112

Claims 11-20, 33, 35 and 36 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner contends that it is not clear what the term "image" in "multi-dose image" and "single-dose image" is meant to encompass.

Without admitting to the propriety of the rejection, Applicants have canceled claims 11-20, 33, 35 and 36 rendering the rejection moot.

Claim Rejections – 35 USC § 102

Claims 1, 9 and 31 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Gao et al. (WO 01/40455A2, "Gao"). The Examiner contends that Gao discloses live, recombinant adenovirus vectors for pharmaceutical use comprising a preservative, such as chlorobutanol.

In response, Applicants have amended claims 1, 9 and 31 to recite a concentration range of chlorobutanol from 0.25% to 0.6% (w/v). As Gao does not teach any concentration range of chlorobutanol, Gao does not anticipate the present invention. See MPEP § 2131.

Accordingly, Applicants respectfully submit that rejection has been obviated.

Claim Rejections – 35 USC § 103

Claims 2, 10-12, 19-22, 29, 30 and 32-36 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gao as applied to claims 1, 9 and 31 above. As applied to claims 2, 10-12, 19-22, 29, 30 and 32-36, the Examiner alleges that it would obvious to one of ordinary skill in the art and well within the ability of that individual to use an amount of chlorobutanol that is effective for the purpose of preservation without exceeding solubility limit for the formulation. The Examiner further alleges that it would have been obvious to use a vial

to store the contents of the formulation in order to protect the formulation for delivery, storage and subsequent use.

Applicants have amended claim 21 to recite a concentration range of chlorobutanol from 0.25% to 0.6% (w/v) and amended claims 2, 10, 22, 30 and 32 to recite a concentration range of chlorobutanol from 0.4% to 0.6% (w/v). To the extent that the rejection applies to the amended claims, Applicants respectfully submit that claims are not *prima facie* obvious in view of Gao.

Applicants respectfully submit that the prior art does not suggest the desirability of the invention nor provide a reasonable expectation of success. Gao merely recites some commonly known preservatives, some of which are FDA approved, which are known to be used in drug formulations. See Gao, page 19, first paragraph. The ability of these compounds to act as preservatives is based on their use with small molecules. There is no indication that any were tested in any virus formulation. However, the combined teachings of the prior art cast doubt as to whether these preservatives would be useful with live adenovirus formulations.

> The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another.

MPEP § 2143.01.

The compatibility of various preservatives, including chlorobutanol, was tested with measles virus. See IDS Ref. C03, Tables III and IV. A 0.5% concentration of chlorobutanol was found to be destructive to the measles virus. See id. This casts doubt on whether chlorobutanol would be useful as a preservative for a live virus formulation.

A topical fluorescein solution containing 1% chlorobutanol (Fluress, See IDS Ref. C12) was found to be cause a significant reduction in adenovirus titers after 14 days. See IDS Ref. C09, Figure. While this study was examining the survival of adenovirus in a topical fluorescein solution containing chlorobutanol, one of ordinary skill in the art would not expect chlorobutanol to be a useful preservative for adenovirus based on these results.

These references teach away from the desirability of using chlorobutanol as a preservative in live adenovirus formulations.

It is also important to note it could not be reasonably predicted whether preservatives that were known to be useful in FDA approved drugs, typically small molecules, would be useful as preservatives for viruses. This is borne out by Applicants' results testing adenovirus stability in the presence of commonly used preservatives. Out of 10 different preservatives tested with adenovirus, only two, chlorobutanol and benzoic acid were found to provide adenovirus stability. See the specification, Table 5. Benzoic acid was found not to be compatible due to pH concerns. See the specification, paragraph [0065].

Thus, the prior art as a whole does not suggest the desirability of the invention nor provide a reasonable expectation of success. Accordingly, Applicants respectfully submit that Gao does not provide a *prima facie* case of obviousness.

Claims 3-8, 13-18 and 23-28 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gao as applied to claims 1, 2, 9, 11 and 21 above, and further in view of Evans et al. (WO 01/66137A1, "Evans"). The Examiner alleges that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because one would have been motivated to improve the stability of live, recombinant adenovirus particles as taught by Gao by using liquid adenovirus formulations comprising a buffer, sugar, salt, divalent cation, non-ionic detergent, cryoprotectant, and a free-radical scavenger and/or chelating agent to inhibit free radical oxidation because Evans teaches improved stability of adenovirus with such formulations.

As discussed above, Gao does not suggest the desirability of the invention nor provide a reasonable expectation of success. As Evans fails to remedy the deficiencies of Gao, Applicants respectfully submit that present invention is not obvious over Gao in view of Evans.

Accordingly, for the reasons above, Applicants respectfully submit that rejections under 35 U.S.C. 103(a) have been obviated.

CONCLUSION

Applicants believe the claims are in condition for allowance. An early indication of the same is requested. The Examiner is invited to contact Applicants' Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

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